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Researchers pinpoint gene expression changes associated with human cancers

By Nancy Lamontagne

Supported in part by NIEHS, a team of researchers has analyzed the metabolic gene expression changes associated with cancer and identified hundreds of potential drug targets. Unlike previous studies that focused on a few genes involved in tumor metabolism, the new work analyzed gene expression data from 22 types of human tumors.

Bielas received an NIEHS ONES award in 2010, which he uses to study the environmental link between the induction of mitochondrial DNA mutations and cancer, aging, and disease. (Photo courtesy of Jason Bielas)

The new study *(http://www.ncbi.nlm.nih.gov/pubmed/23604282)* showed that gene expression changes associated with tumor-related metabolism vary significantly across tumor types. Cancer cells must reprogram their metabolism to support the synthesis of new cellular components and generate the energy required for uncontrolled proliferation. For example, tumor cells shift from oxidative respiration to aerobic glycolysis.

The researchers hypothesize that the initiation and accumulation of random mutations in nuclear DNA fuels carcinogenesis and the metabolic changes that occur as cancer progresses. “Environmental mutagens, in particular, likely play a substantial role in the origin and incidence of cancer, by damaging DNA and increasing the rate at which mutations accumulate,” said NIEHS Outstanding New Environmental Scientist (ONES) grantee Jason Bielas, Ph.D., *(http://sharedresources.fhcrc.org/content/jason-h-bielas)* who was part of the research team. “Given the critical role of DNA mutations in cancer, a mechanistic understanding of the environmental factors that accelerate mutation should aid in the identification of risk factors and methods that prevent and/or slow disease.”

From global metabolism network to individual reactions

To understand metabolic gene expression in different cancers, the researchers, led by Dennis Vitkup, Ph.D., *(http://vitkuplab.c2b2.columbia.edu/)* at Columbia University, used a large collection of gene expression profiles accumulated over the last decade. They compared gene expression in tumors and corresponding normal tissues at several levels of biochemical organization — the global metabolism network, individual biochemical pathways, and individual enzymatic reactions. Bielas, a researcher at the Fred Hutchinson Cancer Research Center and affiliate assistant professor at the University of Washington School of Medicine, designed and supervised experimental research and data analysis for the metabolic profiling.

The researchers did not find any universal changes in tumor-induced gene expression across the human metabolic network, but they did observe that expression changes in some pathways, including upregulation of nucleotide biosynthesis and glycolysis, appear to be more frequent across tumors. Changes tied to the oxidation phosphorylation pathway were present, but less frequent. When looking at individual biochemical reactions, the analysis revealed many hundreds of metabolic enzymes that underwent significant and tumor-specific expression changes and could, thus, be potential targets for cancer therapies.

The researchers found heterogeneous behavior at all levels of biochemical organization, which means that developing cancer therapies that target metabolism will require an understanding of the metabolic changes that occur in each specific cancer type.

Bielas said that the new results support findings from his previously published NIEHS-funded study *(http://www.ncbi.nlm.nih.gov/pubmed/22685414)* which found that, compared to non-tumor tissue, human colorectal tumor tissue mitochondrial DNA exhibited a decreased prevalence of random single base substitutions induced by oxidative damage. This lower frequency in mutations was associated with a shift in glucose metabolism from oxidative phosphorylation to anaerobic glycolysis. These findings suggest that normal mitochondrial DNA mutation rates may prevent cancer progression, and Bielas hypothesizes that cancer therapies designed to increase mitochondrial DNA damage might suppress malignant growth.

Citation: Hu J, Locasale JW, Bielas JH, O'Sullivan J, Sheahan K, Cantley LC, Heiden MG, Vitkup D. *(http://www.ncbi.nlm.nih.gov/pubmed/23604282)* 2013. Heterogeneity of tumor-induced gene expression changes in the human metabolic network. Nat Biotechnol; doi:10.1038/nbt.2530 [Online 21 April 2013].

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